aliquot and therefore related to the concentration of target molecule in the sample.--

In The Drawings

Please substitute Formal Drawing Sheets 1-4 for the filed informal drawings.

REMARKS

In response to the Office Action of May 21, 2002 in the above described patent application, Claims 1, 14-15 and 17-18 are amended and new Claim 45 is added hereby. Applicant submits herewith an Abstract and Formal Drawings. The amended and new claims, in versions both clean and marked-up to show changes, and the Abstract are also submitted on separate attached pages.

The specification was objected to for having informal drawings. Applicant submits herewith Formal Drawing Sheets 1-4.

The Examiner has acknowledged Applicant's election of the now-pending claims 1-28, and 33 without traverse. Below we demonstrate why the pending claims 1-28, 33 and 45 are now in condition for allowance.

The subject matter herein is allowable over the art of record.

As a preliminary matter it should be noted that pending claims 1-28, 33 and 45 are directed to a method for quantitatively assaying one or more target molecules in a sample (see for example, the preamble of claim 1) comprising adding nucleic acid aptamer specific for each target molecule to the sample (element a of claim 1), allowing substantially all the target molecules to be bound to aptamer (element b of claim 1), removing unbound aptamer from the sample (element c of claim 1) , and using a quantitative replicative procedure to determine a quantity of for each kind of bound aptamer remaining in the sample (element d of claim 1). The method provides a "quantitative" assay for each kind of target molecule, i.e. the result is a determination for each target molecule of a number that corresponds to its abundance or concentration in the sample. See for example, Application at page 10, lines 8-10.

In Paragraph 10 of the Office Action, claims 1, 2, 6, 7, 15 and 20 are rejected as anticipated under 35 USC §102(b) in view of US 5,756,291 to Griffin et al. (hereinafter "Griffin"). The Griffin reference cited by the Examiner is not concerned with using aptamers for quantitatively assaying target molecules. Instead, Griffin is concerned with the recovery and deduction of aptamers which bind specifically to desired targets, Col. 12, lines 19 et seq. Griffin also suggests the use of aptamers as a separation means for retrieving targets (at Col. 12, lines 33-35) and for diagnosis (Col. 12, line 38). Thus Griffin is concerned with identification of aptamers, but not with their use for quantitative analysis of target molecules. In fact, Griffin does not use or suggest using the aptamers which he identifies for the purpose of directly quantifying the amount of bound target molecule by quantifying the amount of bound replicable aptamer using a quantitative replicative procedure of the kind taught by the invention as claimed. Therefore it is believed that the rejection stated in Paragraph 10 should be reconsidered, withdrawn and the claims allowed.

In Paragraph 11, part I of the Office Action, claims 3, 4, 5, 8-14 and 24 are rejected as anticipated under 35 USC §103 in view of the Griffin reference in combination with the teachings of US Patent No. 6,180,415 to Schultze et al. Applicant respectfully traverses the rejection and urges the Examiner to reconsider, withdraw the rejection and allow the claims. As discussed hereinabove, Griffin relates to methods of identifying useful aptamers. Griffin also describes using aptamers identified by his methods for various diagnostic and separation techniques. Schultze relates to the use of plasmon resonant particles for detection of target molecules in a field by illuminating the field and detecting spectral emissions characteristic of the individual plasmon resonant entities, Col. 2, lines 57-60. Although this reference identifies in its background that quantitative analysis is part of the aim of analyte diagnostic tests and methods (Col. 1, lines 16-20), and that current methods do not permit detection of "single (or only a few) molecular events" (Col. 2, lines 17-20), it addresses analysis only in the context of plasmon resonant technology and even there it appears to be primarily of a qualitative nature. Schultze does not cure Griffin's deficiency as it relates to the claims from which the instant claims depend, in that it does not teach the use of a quantitative replicative procedure for the purpose of directly quantifying the amount of a bound aptamer and

thereby directly quantify the amount of target molecule. There is nothing in Griffin alone, as discussed above, to suggest the claimed subject matter, and Schultze does not add to Griffin with respect to the claimed subject matter.

Since the instant claims are dependent from claims which themselves are not made obvious by this inappropriate and deficient combination of references, they too are allowable over the art. Therefore it is believed that the rejection stated in Paragraph 11, part I should be reconsidered, withdrawn and the claims allowed.

In Paragraph 11, part II, claims 16-17, 24-28 and 33 are rejected as obvious under 35 USC §103 in view of Griffin, Schultze and PCT Publication WO96/10576 from Wiegand et al. The addition of the Wiegand reference fails to cure the deficiencies of the combination of references as detailed hereinabove. As discussed hereinabove, Griffin relates to methods of identifying aptamers which may be used for various diagnostic and separation techniques. Schultze relates to the use of plasmon resonant particles for detection of target molecules in a field by illuminating the field and detecting spectral emissions characteristic of the individual plasmon resonant entities. Although Wiegand does teach using SELEX in vitro evolutionary technology for identifying and producing nucleic acid ligands to IgE having varying properties (see Wiegand, page 5, line 26 et seq. and page 9, lines 2-6), Wiegand does not describe using quantitative replicative procedures to directly quantify the amount of a bound target molecule in the original sample. Since there is nothing in Griffin and Schultze either alone or combined, as discussed above, to suggest the claimed subject matter, and Wiegand does not add to Griffin and Schultze with respect to the claimed subject matter, it is believed that the rejection stated in Paragraph 11, part II should be reconsidered, withdrawn and the claims allowed.

In Paragraph 11, part III, claims 19, 21-23 are rejected as obvious under 35 USC §103 in view of Griffin, Schultze and US Patent No. 6,054,274 to Sampson et al. (hereinafter "Sampson"). Although the focus of Sampson is on the amplification of nucleic acid signals in PCR reactions using a rolling circle replication mechanism and a bidirectional primer (Col. 3, lines 23-46), there is no disclosure or suggestion of harnessing, or how to harness, PCR techniques for performing the quantitative analysis of targeted molecules by replicative procedures as is now claimed. Nor is there any

suggestion of or motivation for combining the disclosed methods for amplification of sequences by serial hybridization and polymerization with Griffin's methods for identifying useful aptamers or Schultze's use of plasmon resonant particle technology for detecting or identifying the presence of target molecules. Detection and identification are not the primary objective of the present invention. The primary goal as claimed is direct quantification, which the cited references do not teach, alone or combined, however improperly so. The rejected claims are dependent from claims which are not obviated by the combination of references and therefore are themselves not obviated thereby. Therefore it is believed that the rejection stated in Paragraph 11, part III should be reconsidered, withdrawn and the claims allowed.

The application satisfies requirements under 35 U.S.C. § 112

We show below that, although the Examiner has faulted the application on grounds of indefiniteness and non-enablement, the requirements of §112 are fully satisfied by the application as amended herewith.

In Paragraph 7, subparagraph B of the Office Action, the Examiner contends that a detection step must be recited. Similarly, Paragraphs 8 and 9 of the Office Action reject all of the pending claims 1-28 and 33 as indefinite under §112, second paragraph for omitting "essential steps" and under §112, first paragraph for being based on a non-enabling disclosure. Applicant notes for the record that, in Claim 1, for example, steps are recited beginning with addition of aptamer in step (a), allowing binding with aptamer in step (b), separating unbound aptamer to recover aptamer that is bound to target molecules in step (c) and then using a quantitative replicative procedure with respect to the bound aptamer to determine a quantity related to the concentration of target molecule. It is clear that the concept of detection is implicit in these steps, to the extent that target molecule is present in the sample. With respect to the Examiner's requirement that Applicant specifically use the word "detection", the rejection is hereby traversed. An abundance of case law affirms that an applicant may be his own lexicographer e.g., *Fonar Corp. v. Johnson & Johnson*, 821 F.2d 627, 3 USPQ2d 1109 (Fed. Cir. 1987), 484 U.S. 1027 (1988); *ZMI Corp. v. Cardiac Resuscitator Corp.*, 844 F.2d 1576, 6 USPQ2d 1557 (Fed. Cir. 1988) "[T]he terms of a claim will be given their ordinary meaning,

unless it appears that the inventor used them differently" and "the specification aids in ascertaining the scope and meaning of the language employed in the claims inasmuch as words must be used in the same way in both the claims and the specification."

The alleged "missing essential steps" fall into the same category, since the claim clearly recites steps that can be followed by a person of ordinary skill in the art without undue experimentation and the recited steps are clearly a complete process for conducting the claimed quantitative assay. Moreover, the specification (for example, at page 20, lines 14-26) and Figures 1 and 3 clearly show that adding aptamer to a sample (recited in step a of claim 1) brings the aptamer into contact with a target molecule, if the target molecule is present in the sample solution. The next "essential" step, detection, is accomplished (to the extent target molecule is present) in allowing aptamer to bind with target molecule (recited in step b of claim 1) and prior to the remaining steps to achieve quantification pursuant to the assay. In view of Applicant's recital of claim steps which encompass the activities the Examiner views as "essential", Applicant can only conclude that the Examiner takes issue with Applicant's choice of words to describe these activities. But *Fonar Corp.v. Johnson & Johnson, supra*, and *ZMI Corp. v. Cardiac Resuscitator Corp., .supra.*, among countless others, reaffirm the applicant's right to be his own lexicographer.

In Paragraph 9, the Examiner raises the issue of a nonenabling specification under §112 first paragraph, but merely repeats the allegations of missing steps in the claims (adequately addressed hereinabove), rather than identifying alleged deficiencies in the specification. On the assumption that the Examiner intended to allege that particular terms missing from the claims are also missing from the specification, whether or not the exact words desired by the Examiner appear in the specification is irrelevant. What is relevant and wholly dispositive of the issue is the fact that the functions which those terms describe are clearly found in the descriptions of the exemplary embodiments, and that one of ordinary skill in the art would have more than enough information about the invention to enable him to know what it is and to carry it out. Whereas Applicant has satisfied his duty to express the claim in words from which one of ordinary skill in the art will know how to do the invention (enablement), when read in light of the specification, and will know what the scope of the claim is as well (see MPEP 2173.02 citing *Solomon*

v. Kimberly Clark Corp., 55 USPQ2d 1279, 1283 (Fed. Cir. 2000), the Examiner has failed in her duty "to establish a reasonable basis to question the enablement provided for the claimed invention" MPEP 2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, 31 USPQ2d 1510, 1513 (Fed. Cir. 1993). Therefore it is believed that the rejections in Paragraph 7, subparagraph B and Paragraphs 8 and 9 should be reconsidered, withdrawn and claims 1-28, 33 and 45 should be allowed.

In Paragraph 7, subparagraph C of the Office Action, the Examiner contends that the term "substantially all" should be removed. Applicant specifically traverses the rejection on the grounds that one of ordinary skill in the art would understand what is meant from reading the disclosure by the term. It would be within the expected ken of one of ordinary skill in the art to decide, based on such factors as desired accuracy, time-temperature reaction kinetics, and other such factors, how and when to proceed from the binding step to the separation step of the claim. The case law makes clear that `[m]athematical precision should not be imposed for its own sake; a patentee has the right to claim the invention in terms that would be understood by persons of skill in the field of the invention.' *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1557 (Fed. Cir.), *cert. denied*, 518 U.S. 1005 (1996). The "use of terms of degree, such as 'substantially,' in patent claims does not necessarily render the claims indefinite. In fact, the Court of Appeals for the Federal Circuit has recognized that such 'words are ubiquitous in patent claims.' " *Bausch & Lomb*, 64 F.Supp.2d at 240 (quoting *Andrew Corp. v. Gabriel Electronics, Inc.*, 847 F.2d 819, 821 (Fed. Cir.) (referring to, inter alia, phrase `substantially equal'), *cert. denied*, 488 U.S. 927 (1988). See also *Amtel Corp. v. Information Storage Devices, Inc.*, 997 F. Supp. 1210, 1228 (N.D. Cal. 1998) (holding term 'substantially all' not to be indefinite). Accordingly, the rejections stated in Paragraph 7, subpara. C, and Paragraphs 8 and 9 should be reconsidered, withdrawn and the claims allowed.

New claim 45, is similar to Claim 1, but removes the term "substantially all" for a reason different from that suggested by the Examiner. In particular, since the techniques disclosed rely on the correspondence of aptamer with target molecules, only one class of embodiments need depend upon detection of approximately 100% of target molecules. It is contemplated that using the teachings of the description herein, one may still

introduce an excess of aptamer to the sample and utilize approaches known in the art (including time-temperature kinetic behavior of the relevant molecules in the pertinent fluid environment) to estimate the percentage of target molecule (which may potentially fall substantially below 100%) that has been bound to aptamer at a particular time. This percentage can be used to adjust calculations of concentration in later steps. Although the scope of the amended claim has been expanded by this amendment, the limitation of the amended element is well supported by the disclosure.

In Paragraph 7, subparagraph D of the Office Action, the Examiner rejects Claims 3 and 4 are indefinite. Applicant respectfully traverses the rejection on the grounds that it would be clear to one of ordinary skill in the art from a reading of the specification that the reference to dissociation constants of the target molecule relates to an objective but dynamic lower limit of concentration of the target molecule. Applicant respectfully asserts that the claims are easily understood in light of the specification and amendment is not required. Therefore it is believed that the rejection stated in Paragraph 7, subpara. D should be reconsidered, withdrawn and the claim allowed.

In Paragraph 7, subparagraphs E, F and G of the Office Action, the Examiner rejects Claims 14, 15, 17 and 18 as indefinite for such reasons as imprecise usage of Markush grouping language. Applicant's amendments to the claims address these issues, which barely rise above the level of typographical errors, in a way which should not be construed as affecting the scope of these claims in any way.

In Paragraph 7, subparagraph A, claims 1-28 and 33 have been rejected as indefinite under §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. By the amendment of claim 1, Applicant has clarified that second sample is what is recovered after separating unbound aptamer from the first sample, and contains aptamer specific for target molecules which is bound to target molecules. This feature was inherent in the claim as originally submitted and no change in scope of the claim has been made by this change. Therefore it is believed that the rejection stated in Paragraph 7, subpara. A should be reconsidered, withdrawn and the claims allowed.

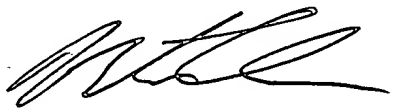
Further Matters

The Examiner has acknowledged and entered into the record the references cited by Applicant's IDS, filed on 7/26/00. Applicant has noted that the IDS inadvertently failed to list one reference cited by the specification at Page 2, lines 25-28. A copy of the reference is in the process of being obtained and will be submitted with a Supplemental IDS as soon as possible.

Conclusion

In view of the foregoing comments and amendments, it is believed that the application has been put into condition for allowance and early notice to that effect is respectfully solicited.. The Examiner is respectfully urged to reconsider the rejections, withdraw them and allow the application with amended claims 1-28, 33 and 45. If the Examiner believes that further issues remain outstanding, she is respectfully requested to contact Applicant's representative by telephone to see if the issues can be resolved telephonically or in person. Please charge any additional fee required for the timely consideration of this application to Deposit Account No. 19-4972.

Respectfully submitted,



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September 23, 2002

02331/00111 214165.1

Amended Claims Marked to Show Revisions

--1. (Amended) A method for quantitatively assaying one or more target molecules in a first sample, comprising:

(a) adding to the first sample, a preparation of a nucleic acid aptamer specific for each target molecule;

(b) allowing substantially all of the target molecules in the first sample to bind with [the] aptamer[s];

(c) separating unbound aptamer[s] from the first sample by contacting the sample of step (b) with immobilized ligands, [wherein] thereby binding the ligands [bind] to [the]unbound aptamer[s;], so as to

[(d)] recover[ing] a second sample [containing the] of aptamer bound to target molecules; and

[(e)](d) using a quantitative replicative procedure to determine a quantity [related to the concentration] of [the] aptamer specific for each target molecule in the second sample and therefore related to the concentration of target molecule[s] in the first sample.--

--14. (Amended) A method according to claim 13, wherein the first sample is selected from the group of tissues consisting of organ tissue, muscle tissue, bone tissue, connective tissue, fetal tissue, and placental[,] tissue.--

--15. (Amended) A method according to claim 1, wherein the sample is a biological fluid selected from the group consisting of blood, lymph, urine, sputum, joint [including] fluid, spinal fluid, and saliva.--

--17. (Amended) A method according to claim 16, wherein the environmental sample is obtained from a source selected from the group consisting of plants, water, food beverages (including milk), and industrial waste.--

--18. (Amended) A method according to claim 1, wherein the immobilized ligand is immobilized on a support matrix selected from the group consisting of resins, beads, [including] magnetic beads, gels, cellulose and silica.--

Amended Claims (Clean Set)

--1. (Amended) A method for quantitatively assaying one or more target molecules in a first sample, comprising:

(a) adding to the first sample, a preparation of a nucleic acid aptamer specific for each target molecule;

(b) allowing substantially all of the target molecules in the first sample to bind with aptamer;

(c) separating unbound aptamer from the first sample by contacting the sample of step (b) with immobilized ligands, thereby binding the ligands to unbound aptamer, so as to recover a second sample of aptamer bound to target molecules; and

(d) using a quantitative replicative procedure to determine a quantity of aptamer specific for each target molecule in the second sample and therefore related to the concentration of target molecule in the first sample.--

--14. (Amended) A method according to claim 13, wherein the first sample is selected from the group of tissues consisting of organ tissue, muscle tissue, bone tissue, connective tissue, fetal tissue, and placental tissue.--

--15. (Amended) A method according to claim 1, wherein the sample is a biological fluid selected from the group consisting of blood, lymph, urine, sputum, joint fluid, spinal fluid, and saliva.--

--17. (Amended) A method according to claim 16, wherein the environmental sample is obtained from a source selected from the group consisting of plants, water, food beverages, and industrial waste.--

--18. (Amended) A method according to claim 1, wherein the immobilized ligand is immobilized on a support matrix selected from the group consisting of resins, beads, magnetic beads, gels, cellulose and silica.--

--45. (New) A method for quantitatively assaying one or more target molecules in a first sample, comprising:

(a) adding to the first sample, a preparation of a nucleic acid aptamer specific for each target molecule;

(b) allowing target molecules in the first sample to bind with aptamer;

(c) separating unbound aptamer from the first sample by contacting the sample of step (b) with immobilized ligands, thereby binding the ligands to unbound aptamer, so as to recover a second sample of aptamer bound to target molecules; and

(d) using a quantitative replicative procedure to determine a quantity of aptamer specific for each target molecule in the second sample and therefore related to the concentration of target molecule in the first sample.--